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Review article

Drug repositioning

Man Mohan Mehndiratta [a,*], Swati Anil Wadhai [b], Brij Kishor Tyagi [c], Natasha Singh Gulati [b], Madhu Sinha [b]

[a] Department of Neurology, Janakpuri Super Specialty Hospital, Janakpuri, New Delhi 110058, India
[b] Department of Pathology, Janakpuri Super Specialty Hospital, Janakpuri, New Delhi 110058, India
[c] Janakpuri Super Specialty Hospital, Janakpuri, New Delhi 110058, India

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ABSTRACT

Rapid advances in pharmacotherapy and bioinformatics has led to the discovery and growing popularity of drug repositioning which includes re-investigating or recycling of existing drugs for new indications. There are innumerable advantages as well as challenges of drug repositioning. Since de-novo drug discovery takes plenty of time, effort and money, it has proved to a preferred alternative strategy for accelerated drug discovery. Moreover it is relatively inexpensive and carries minimal risk due to availability of previous pharmacological, safety and toxicology data. The strategies used are Known drug – new target/ Drug focus/Drug-centric, Known target- new indication/ Target focus/Target-centric and Disease focus/Disease-centric. Drug repositioning is a new breakthrough strategy to benefit patients by offering safer and effective treatment using shelved drugs.

Drug repositioning is defined as the process of finding a new indication for an approved drug or abandoned pharmacotherapies.[1] It identifies new indications of existing drugs and the application of the newly identified drugs to the treatment of diseases other than the drug's original indication.[2] It involves analysis of drugs that have already been sanctioned for treatment of other diseases or whose targets have already been identified. Other synonyms are drug repurposing, drug rescue, redirecting, re-profiling, re-tasking, therapeutic switching and indication switching.[3] It emerged primarily in the early 1990s as an accidental discovery but lately due to development of new advents and tools the process has become more systematic. Repurposing of older drugs can fulfill vast unmet medical needs. It is an alternative to conventional de novo drug discovery and development. Repositioning is an accelerated approach for drug discovery because existing drugs have already passed pharmacokinetic and clinical analysis.

Presently drug repositioning project plays a pivotal role in the de novo drug discovery ventures of the pharmaceutical industry. The process of new drug development is tricky, time consuming and expensive. The pharmaceutical companies have not balanced output and the tremendous increase in research and development expenditure.[4] This difference in productivity exists even though pharmaceutical companies have invested stupendous amounts in novel drug discovery technologies.[5] The pharmaceutical companies today are facing downhill productivity with increased research and development expenditure. The pharmaceutical industry faces multiple challenges like, higher rates of attrition, drug safety issues, high regulatory pressures, expiring patent protection, and competition from generic drugs.[6] The pharmaceutical companies are considering drug repositioning for accelerated drug discovery as it carries minimal risk of failure and is relatively inexpensive. Moreover they are always looking for developing drugs products which are economical, and carry limited risk strategy along with protection of existing products from competition and extension of their patent protection time.[7] Drug repositioning is a low risk, high reward strategy as compared to de novo drug discovery, which is high risk, high reward strategy. There are 2000 failed drugs sitting that have the potential to develop into successful repositioned drugs. The list of failed drugs is increasing at the rate of approximately 150–200 compounds per year.[8,9]

There are innumerable advantages of drug repositioning. It helps to recoup the existing expenditure, saves time and money with better implementation of sources. The cost to re-launch repositioned drug is quite reasonable (~8.4 million USD), whereas

* Corresponding author at: President Asian and Oceanian Association of Neurology, Janakpuri Super Specialty Hospital, C-2/B, Janakpuri, New Delhi 110058, India.
E-mail addresses: mmehndi@hotmail.com, mmehndi@gmail.com (M.M. Mehndiratta), swatiwadhai@gmail.com (S.A. Wadhai), drtyagispm@gmail.com (B.K. Tyagi), dr.ngulati@gmail.com (N.S. Gulati), madhushekharnath@rediffmail.com (M. Sinha).

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cost to re-launch the new formulation is extremely expensive (~41.3 million USD). The development of new drug costs more than 2.6 billion USD.[10] So to launch the repositioned drug successfully to the market is quite economical than that of new drug. In clinical trials, repositioned drugs compete with non-repositioned drugs in terms of efficacy rather than safety. Repurposed drugs escape much of the developmental cost than the traditional drug discovery due to availability of earlier pharmacokinetic, bioavailability, safety and toxicology data. Approximately 1 in 10,000 new drug that enters the clinical research and trial process, genuinely makes it to the market and roughly 30% of the drugs researched in clinical trials fail to qualify due to inefficacy.[9,11,12] Thus repositioning ensures significant time and capital saving.

De novo drug discovery, right from the target identification to its development and approval takes almost 10–17 years whereas approval of an existing drug takes 3–12 years. In standard drug discovery, target discovery takes 2–3 years, screening and designing chemicals with biological activity takes 6 months to 1 year, lead optimization takes 1–3 years, 1–2 years to confirm drug ADMET (absorption distribution, metabolism, excretion and toxicity) properties using animal models, 5–6 years in clinical trial to determine drug safety and efficacy and 1–2 years for licensing. But in case of repositioning, compound identification takes 1–1.5 years, compound acquisition takes 0–1.5 years, preclinical development 0–1 year, clinical trials 1–6 years, and 1–2 years for licensing.[1] Few studies have shown that approval of a repositioned drug can be achieved in only 4 years.[13] Thus by reducing length of time for development and re-launch of repurposed drug we can provide accelerated treatment options to the patients. Success rates for repurposed drugs are higher as compared to de novo drug discovery. Success rate for repurposed drugs was approximately 30% in recent years and was recently approved by the US FDA.[14]

List of successfully repositioned drugs[8,9,11,15–17]:

Drug	Original indication	New indication
Amantadine	Influenza	Parkinsonism
Amphotericin	Antifungal	Leishmaniasis
Aspirin	Inflammation, pain	Anti-platelet, stroke
Amitripyline	Anti-depressant	Neuropathic pain
Azathioprine	Rheumatoid arthritis (RA)	Multiple sclerosis (MS), inflammatory bowel disease (IBD) and organ transplants
Bupropion	Depression	Smoking cessation and weight-loss (combi-therapy)
Bimatoprost	Glaucoma	Eyelash growth
Bromocriptine	Parkinson's disease	Diabetes mellitus
Bleomycin	Antibiotic	Cancer
Bromocriptine	Parkinson's disease	Type II diabetes
Buprenorphine	Pain	Drug treatment
Colchicine	Gout	Recurrent pericarditis and familial mediterranean fever
Clofazime	Tuberculosis	Leprosy
Canakinumab	Rheumatoid arthritis	Muckle–Wells syndrome
Cyclosporine	Organ transplant rejection	Psoriasis and rheumatoid arthritis
Colesevelam	LDL-lowering	Type II diabetes
Crizotinib	Clinical trials for anaplastic large-cell lymphoma	Non-small cell lung carcinoma (NSCLC)
Cycloserine	Tuberculosis	CNS disorders
Dimethyl fumarate	Psoriasis	Multiple sclerosis
Dapoxetine	Antidepressant	Premature ejaculation
Doxepin	Antidepressant	Atopic dermatitis
Donepezil	Alzheimer's disease	Dementia
Duloxetine	Depression	Stress, fibromyalgia, urinary incontinence and chronic musculoskeletal pain
Etanercept	Rheumatoid arthritis	Plaque psoriasis
Everolimus	Immunosuppressant	Pancreatic neuroendocrine tumors
Eflornthine	Cancer	Hirsutism and sleeping sickness
Fluoxetine	Antidepressant	PMDD (premenstrual dysphoric disorder)
Finasteride	Hypertension	Benign prostatic hyperplasia and male pattern baldness
Galantamine	Chronic fatigue syndrome	Alzheimer's disease
Gabapentin	Epilepsy	Neuropathic pain
Glycopyrronium	Anti-ulcer	Chronic obstructive pulmonary disease (COPD)
Gemcitabine	Anti-viral	Various cancers
Hydroxychloroquine	Malaria	Lupus and rheumatoid
Histrelin	Prostate cancer	Precocious puberty
Imatinib	CML	Gastrointestinal stromal tumors
Ibuprofen	Inflammation, pain	Osteoarthritis (OA), rheumatoid arthritis (RA), headache and migraine
Iproniazid	Tuberculosis	Antidepressant
Imfliximab	Autoimmune diseases	Crohn's disease
Lomitapide	Hypercholesterimia	HoFH (homozygous familial hypercholesterolemia)
Methotrexate	Cancer	Psoriasis and RA
Miltefosine	Cancer	Visceral leishmaniasis
Minoxidil	Hypertension	Male pattern baldness
Milnacipran	Anti-depressant	Fibromyalgia
Naltrexone	Opioid/alcohol addiction	Weight-loss (combi-therapy)
Nelfinavir	Acquired immunodeficiency syndrome (AIDS)	In clinical trials for multiple cancers
Onabotulinumtocin	Facial spasm	Chronic migraine, cervical dystonia and facial cosmetics
Paroxetine	Antidepressant	Menopausal hot flashes
Paclitael	Various cancers	Stent re-stenosis prevention
Plerixafor	AIDS/HIV	Lymphoma and multiple myeloma
Pertuzumab	Various cancers	HER-2 + breast cancer
Pregabalin	Anticonvulsant and neuropathic pain	Fibromyalgia
Pramipexole	Parkinson's disease	Restless leg syndrome
Propranolol	Hypertension	Tremors, angina and migraine prophylaxis
Raloxifene	Osteoporosis	Breast cancer

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